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| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
|---|-------------|----------------------|---------------------|------------------|
| 09/328,975 | 06/09/1999 | JOHN A. WOLFF | MIRUS009 | 7574 |
| 25032 | 7590 | 10/06/2005 | EXAMINER | |
| MIRUS CORPORATION 505 SOUTH ROSA RD MADISON, WI 53719 | | | SCHNIZER, RICHARD A | |
| | | | ART UNIT | PAPER NUMBER |
| | | | 1635 | |

DATE MAILED: 10/06/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

| | | |
|------------------------------|--|-------------------------|
| Office Action Summary | Application No. | Applicant(s) |
| | 09/328,975 | WOLFF ET AL. |
| | Examiner Richard Schnizer, Ph. D | Art Unit 1635 |

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) Responsive to communication(s) filed on 22 July 2005.
- 2a) This action is **FINAL**. 2b) This action is non-final.
- 3) Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) Claim(s) 1,3 and 5-8 is/are pending in the application.
- 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) Claim(s) _____ is/are allowed.
- 6) Claim(s) 1,3 and 5-8 is/are rejected.
- 7) Claim(s) _____ is/are objected to.
- 8) Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) The specification is objected to by the Examiner.
- 10) The drawing(s) filed on 09 June 1999 is/are: a) accepted or b) objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
a) All b) Some * c) None of:
1. Certified copies of the priority documents have been received.
2. Certified copies of the priority documents have been received in Application No. _____.
3. Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

| | |
|---|---|
| 1) <input type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413) |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | Paper No(s)/Mail Date. _____. |
| 3) <input type="checkbox"/> Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____. | 5) <input type="checkbox"/> Notice of Informal Patent Application (PTO-152) |
| | 6) <input type="checkbox"/> Other: _____. |

DETAILED ACTION

An amendment was received and entered on 7/15/05.

Claims 1, 3, and 5-8 remain pending and are under consideration in this Office Action.

Rejections Withdrawn

The double patenting rejections over US Patents 6,881,576, 6,740,643, 6,740,336, and 6,818,626 are withdrawn in view of the terminal disclaimers filed 7/15/05. The provisional double patenting rejection over application serial number 10/795,679 is withdrawn in view of the terminal disclaimer filed 7/15/05.

The previous rejections under 35 USC 112 second are withdrawn in view of Applicant's amendments.

Claim Rejections - 35 USC § 102/103

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless -

(f) he did not himself invent the subject matter sought to be patented.

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

Claims 1, 3, and 5-8 stand rejected under 35 U.S.C. 102(f) as anticipated by or, in the alternative, under 35 U.S.C. 103(a) as obvious over U.S. Patent No. 6,881,576.

Claim 1 of '576 is drawn to:

1. A process for enhancing delivery of a polyion to a cell, comprising: forming a polyampholyte having a net charge, in the presence of a polyion; and, delivering the complex into a cell.

The specification, in support of this claim, discloses at column 6, lines 44-56 Example 1 which is directed to a general procedure for the formation of a polyampholyte in the presence of DNA:

General procedure for the formation of the polyampholyte in the presence of DNA. (Crosslinking of polycation and polyanion layers on the DNA/PLL/SPLL particles using 1[3-(dimethylamino)propyl]-3-ethyl carbodiimide (EDC) and sulfo-N-hydroxysuccinimide (SNHS). Plasmid DNA (pCILuc) and PLL (M.w. 46 kDa) were mixed in a charge ratio 1:3 (100 ug and 190 ug respectively in 0.5 ml of 20 mM MES, pH 6.5. Succinylated PLL (SPLL) was activated with EDC/SNHS in 50 ul of unbuffered solution at pH 5.0 for 10 min (690 ug SPLL, 1.4 mg EDC, 700 ug SNHS). Then the DNA/PLL complex and activated SPLL were mixed (DNA:PLL:SPLL charge ratio 1:3:10) and the mixture was incubated overnight at room temperature.

Accordingly claim 1 of '576 embraces a method of forming a complex between a nucleic acid and a polycation wherein the complex has a net charge less negative than the nucleic acid, and subsequently associating with that complex a polyanion in sufficient amount to give the complex a net negative charge. The instant claims do not exclude the step of forming a polyampholyte by crosslinking the polyanion to the polycation, so '576 claim 1 and dependents render it obvious, particularly in view of '576 claim 6 which requires delivery of the complex *in vivo*. The limitations of instant claim 3 (polycation = polylysine or polyethylenimine) are found in '576 claim 2, as is the limitation of instant claim 6, requiring block copolymers. The limitations of instant claim 5 are found in '576 claim 4. Claim 8 is included in this rejection because the ternary complex of '576

Example 1 appears to comprise a polyanion of at least 80 monomeric units. The polyanion is disclosed at column 6, line 51 as succinylated PLL, and PLL is defined at column 6, line 49 as having a molecular weight of 46 kDa. Assuming a monomer molecular weight of 128 g/mol per lysine monomer, the PLL used is about 360 monomers in length.

However, the inventors of '576 are Jon Wolff, James Hagstrom, Vladimir Budker, and Vladimir Trubetskoy, whereas the instant application names these inventors as well as Paul Slattum, Aaron Loomis, and Sean Monahan. As a result it is not clear who has invented the instantly claimed invention.

Claims 1, 3, and 6-8 stand rejected under 35 U.S.C. 102(f) as anticipated by or, in the alternative, under 35 U.S.C. 103(a) as obvious over U.S. Patent No. 6,740,643 in view of Lee et al (WO 97/00965, published 1/9/97).

Claim 1 of '643 is drawn to:

A process for obtaining an expression product by delivering a polynucleotide to a cell, comprising: a) associating a noncovalent amphiphilic polyelectrolyte, a cyclodextrin, and a polynucleotide thereby forming a complex, wherein the noncovalent amphiphilic polyelectrolyte consists of a polymeric amphiphile binding agent and charged amphiphiles; and b) delivering the complex to the cell; and, c) expressing the polynucleotide.

It is clear in view of the specification at the paragraph bridging columns 16 and 17 that claim 1 embraces a method of forming a complex between polylysine and a nucleic acid in the presence of a cyclodextrin, and subsequently recharging the complex by addition of a cyclodextrin-epichlorohydrin copolymer that is rendered polyanionic by addition of 4-t-butylbenzoic acid.

'643 does not explicitly teach that recharged complexes must have a net negative charge.

Lee taught that targeted cationic nucleic acid delivery complexes allow non-specific, non-targeted cellular uptake due to the fact that cells generally have a negative surface charge. Despite the presence of a targeting ligand, the charge attraction between positively charged complexes and negatively charged cells leads to non-specific interactions and uptake. Lee taught that this problem could be avoided by rendering targeted delivery complexes negative in net charge. See page 2, lines 11-16, and page 9, lines 18-25.

In view of the '643 specification at column 23, line 51 to column 4, line 50, the claimed compositions may comprise targeting signals. As a result it would have been obvious to one of ordinary skill in the art at the time of the invention to recharge a targeted polycation/nucleic acid complex by addition of an anionic cyclodextrin-epichlorohydrin copolymer, and to adjust the amount of anionic copolymer added such that the final charge of the recharged complex was negative. One would have been motivated to do so in order to increase the efficiency of targeting as taught by Lee above.

Claim 8 is included in this rejection because the '643 specification defines "polymer" at column 26, lines 57-60 as having more than 80 monomers. The term "copolymer" is used to describe the polyanion disclosed at the paragraph bridging columns 16 and 17, so it is considered to have more than 80 monomers.

The inventors of '643 are Jon Wolff, James Hagstrom, Vladimir Budker, Paul Slattum, David Rozema, and Sean Monahan, whereas the instant application names these inventors, with the exception of Rozema, as well as Vladimir Trubetskoy and Aaron Loomis,. As a result it is not clear who has invented the instantly claimed invention.

Claims 1, 3, and 5-7 stand rejected under 35 U.S.C. 102(f) as anticipated by or, in the alternative, under 35 U.S.C. 103(a) as obvious over rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over U.S. Patent No. 6,740,336.

Claim 1 of '336 is drawn to:

A process for generating multilayer particles for delivering a polynucleotide to cell, comprising: condensing a polymer with an oppositely charged polymer to form a particle; and, sequentially adding oppositely charged polymers at the particle forming at least three layers of polymers wherein at least one of the polymers is the polynucleotide.

The specification discloses that the first recited polymer may be a nucleic acid, the second a polycation, and the third, used to recharge the polycation/nucleic acid complex, may be any of the polyanions in instant claims 5-7. See e.g. column 5, lines 1-14:

A wide a variety of polyanions can be used to recharge the DNA/polycation particles comprising: succinylated PLL, succinylated PEI (branched), polyglutamic acid, polyaspartic acid, polyacrylic acid, polymethacrylic acid, polyethylacrylic acid, polypropylacrylic acid, polybutylacrylic acid, polymaleic acid, dextran sulfate, heparin, hyaluronic acid, polysulfates, polysulfonates, polyvinyl phosphoric acid, polyvinyl phosphonic acid, copolymers of polymaleic acid, polyhydroxybutyric acid, acidic polycarbohydrates, DNA, RNA, negatively charged proteins, pegylated derivatives of above polyanions, pegylated derivatives carrying specific ligands, block and graft copolymers of polyanions, any hydrophilic polymers (PEG, poly(vinylpyrrolidone), poly(acrylamide), etc), and other water-soluble polyanions.

The specification teaches that the polycation may be polylysine or polyethylenimine. See column 6, lines 6-12 and paragraph bridging columns 11 and 12. Claim 6 requires that the particle formed must be negatively charged. As a result the methods of instant claims 1, 3, and 5-7 are not patentably distinct from those of claims 1-3 of '336.

The inventors of '336 are Jon Wolff, James Hagstrom, Vladimir Budker, Vladimir Trubetskoy, So Chun Wong, and Jason Klein, whereas the instant application names these inventors, with the exception of Wong and Klein, as well as and Aaron Loomis, Sean Monahan, and Paul Slattum. As a result it is not clear who has invented the instantly claimed invention.

Claims 1, 3, and 5-8 stand rejected under 35 U.S.C. 102(f) as anticipated by or, in the alternative, under 35 U.S.C. 103(a) as obvious over U.S. Patent No. 6,818,626.

Claims 1-12 of '626 embrace claim 13 which is drawn to:

A process for delivering a polynucleotide to a cell comprising: a) forming a complex consisting of a polynucleotide, and a first molecule wherein one or more chelators are covalently linked to the first molecule b) adding to the complex of a) a solution containing one or more metal ions and a second molecule, to which one or more chelators are covalently linked, wherein coordination of one or more metal ions by one or more of the chelators stabilizes the interaction between the first molecule and the second molecule, wherein the first molecule consists of a polycation and the second molecule consists of a polyanion; and, c) delivering the complex of step b) to the cell.

The polycation may be polylysine or polyethylenimine, and the polyanion may be e.g. polyglutamate or a nucleic acid. See e.g. column 12, lines 6-12. the polymers may be copolymers. See column 4, lines 14-18. Claim 8 is included in this rejection because the '626 specification defines a polymer as consisting of at least 80 monomers. See column 4, lines 14-18. At column 9, lines 50-58, the specification supporting the claims indicates that the anionic polymer containing chelators can be utilized in "recharging"

(another layer having a different charge) the polychelator-polynucleotide complex. The resulting recharged complex can be formed with an appropriate amount of negative charge such that the resulting complex has a net negative charge.

The inventors of '626 are Jon Wolff, James Hagstrom, Vladimir Budker, Vladimir Trubetskoy, Paul Slattum, and Sean Monahan, whereas the instant application names these inventors as well as Aaron Loomis. As a result it is not clear who has invented the instantly claimed invention.

Claims 1, 3, and 5-7 stand provisionally rejected under 35 U.S.C. 102(f) as anticipated by or, in the alternative, under 35 U.S.C. 103(a) as obvious over copending Application No. 10/795,679. Although the conflicting claims are not identical, they are not patentably distinct from each other for the following reasons.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Claim 6 of '679 is drawn to a method of delivering a nucleic acid to a cell comprising condensing a first polyanion with a polycation to form a particle, adding a second polyanion to the particle to form a complex, wherein at least one of the polyanions is the nucleic acid, and contacting the cell with the complex. In view of claim 14, the first polyanion can be the nucleic acid. In view of claims 9 and 20, the final complex may be negatively charged. The polycation may be polylysine or polyethylenimine. See page 6, lines 28-34, or page 9, lines 1-6. The polyanions may

be any of the polyanions of instant claims 5-7. See the specification at page 7, lines 10-19.

The inventors of '679 include the inventors of the instant application: Jon Wolff, James Hagstrom, Vladimir Budker, Vladimir Trubetskoy, Paul Slattum, Aaron Loomis, Sean Monahan, as well as So Chun Wong, and Jason Klein. As a result it is not clear who has invented the instantly claimed invention.

Response to Arguments

Applicant's arguments filed 7/15/05 have been fully considered but they are not persuasive.

At pages 5 and 6 of the response Applicant addresses each of the rejections in turn.

Applicant argues that each rejection relies upon art which was not available as of the filing date of the instant application. This is unpersuasive because MPEP 2137 states that 35 USC 102(f) does not require an inquiry into the relative dates of a reference and the application, and therefore may be applicable where subsections (a) or (e) are not available for references having an effective date subsequent to the effective date of the application being examined.

With regard to the rejection over US Patents 6,881,576, 6,740,643, and 6,818,626, Applicant states that the instant claims encompass polymers that are not polyampholytes or polymers that are not chelators, in other words in each case the instant claims are broader, and so the inventorship is different.

Applicant also argues essentially that the instant claims and '336 patent claims are of noncoextensive breadth, and therefore have different inventors. Applicant argues the same regarding the '679 application.

This is unpersuasive. MPEP 2137.01 (VI states that inventorship is generally "to another" where there are different inventive entities with at least one inventor in common. "[A] joint application or patent and a sole application or patent by one of the joint inventors are [by] different legal entities and accordingly, the issuance of the earlier filed application as a patent becomes a reference for everything it discloses" (Ex parte Utschig, 156 USPQ 156, 157 (Bd. App. 1966)) except where: (A) the claimed invention in a later filed application is entitled to the benefit of an earlier filed application under 35 U.S.C. 120 (an overlap of inventors rather than an identical inventive entity is permissible). In this situation, a rejection under 35 U.S.C. 102(e) is precluded. See Applied Materials Inc. v. Gemini Research Corp., 835 F.2d 279, 281, 15 USPQ2d 1816, 1818 (Fed. Cir. 1988) ("The fact that an application has named a different inventive entity than a patent does not necessarily make that patent prior art."); and (B) the subject matter developed by another person and the claimed subject matter were, at the time the invention was made, owned by the same person or subject to an obligation of assignment to the same person. In this situation, a rejection under 35 U.S.C. 102(f) /103 or 102(g)/103, or 102(e) /103 for applications filed on or after November 29, 1999, is precluded by 35 U.S.C. 103(c). See MPEP § 706.02(l) and § 706.02(l)(1).

Inventors of subject matter not commonly owned at the time of the invention, but currently commonly owned, may file as joint inventors in a single application. However,

the claims in such an application are not protected from a 35 U.S.C. 102(f)/103 or 35 U.S.C. 102(g)/103 rejection. Applicants in such cases have an obligation pursuant to 37 CFR 1.56 to point out the inventor and invention dates of each claim and the lack of common ownership at the time the later invention was made to enable the examiner to consider the applicability of a 35 U.S.C. 102(f)/103 or 35 U.S.C. 102(g)/103 rejection. It is incumbent upon the inventors named in the application, in reply to an inquiry regarding the appropriate inventorship under subsection (f), or to rebut a rejection under 35 U.S.C.102(a) or (e), to provide a satisfactory showing by way of affidavit under 37 CFR 1.132 that the inventorship of the application is correct in that the reference discloses subject matter invented by the applicant rather than derived from the author or patentee notwithstanding the authorship of the article or the inventorship of the patent. See MPEP 706.02 (I).

This Application was filed prior to November 29, 1999, so the patents relied upon in the rejections can be disqualified as prior art under 35 U.S.C. 103(c) if the subject matter of the patents A) qualifies as prior art only under 35 U.S.C. 102(f) or 35 U.S.C. 102(g), and B) was commonly owned with the claimed invention at the time the invention was made. If the subject matter that qualifies as prior art only under 35 U.S.C. 102(f) or 35 U.S.C. 102(g) was not commonly owned at the time of the invention, the subject matter is not disqualified as prior art under 35 U.S.C. 103(c). See OddzOn Products, Inc. v. Just Toys, Inc., 122 F.3d 1396, 1403-04, 43 USPQ2d 1641, 1646 (Fed. Cir. 1997).

To overcome the rejections it is necessary to show that the subject matter claimed herein was not invented by the another, i.e. by inventors named on the other patents or application who are not listed as inventors on the instant application. This can be accomplished by pointing out the inventor and invention dates of each claim and the lack of common ownership at the time of the later invention, or by a showing of common ownership with the claimed invention at the time the invention was made. See MPEP 706.02 (I).

Conclusion

No claim is allowed.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

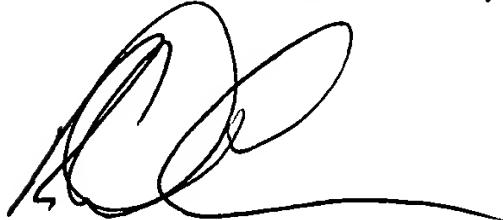
Any inquiry concerning this communication or earlier communications from the examiner(s) should be directed to Richard Schnizer, whose telephone number is 571-

272-0762. The examiner can normally be reached Monday through Friday between the hours of 6:00 AM and 3:30 PM. The examiner is off on alternate Fridays, but is sometimes in the office anyway.

If attempts to reach the examiner by telephone are unsuccessful, the Examiner's supervisor, Andrew Wang, can be reached at (571) 272-0811. The official central fax number is 571-273-8300. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

Patent applicants with problems or questions regarding electronic images that can be viewed in the Patent Application Information Retrieval system (PAIR) can now contact the USPTO's Patent Electronic Business Center (Patent EBC) for assistance. Representatives are available to answer your questions daily from 6 am to midnight (EST). The toll free number is (866) 217-9197. When calling please have your application serial or patent number, the type of document you are having an image problem with, the number of pages and the specific nature of the problem. The Patent Electronic Business Center will notify applicants of the resolution of the problem within 5-7 business days. Applicants can also check PAIR to confirm that the problem has been corrected. The USPTO's Patent Electronic Business Center is a complete service center supporting all patent business on the Internet. The USPTO's PAIR system provides Internet-based access to patent application status and history information. It also enables applicants to view the scanned images of their own application file folder(s) as well as general patent information available to the public.

For all other customer support, please call the USPTO Call Center (UCC) at 800-786-9199.



Richard Schnizer, Ph.D.